REMARKS

Claims 49-65 are pending and under examination. Claims 55 and 63 have been cancelled and claims 53, 54, 61 and 65 have been amended. Following entry of the amendments, claims 49-54, 56-62 and 64-65 will be pending and under examination. Support for the amendments can be found throughout the application as of it priority date. Specifically, support for the amendment to claims 53 and 61 can be found in these claims as originally filed. Claims 53, 54, 61 and 65 have been amended to correct obvious informalities and suggested by the Examiner. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has review the rejections set forth in the Office Action mailed May 4, 2005, and respectfully traverse all grounds for the reasons that follow.

Rejections Under 35 U.S.C. § 112

Claims 49-65 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. In particular, claim 49 stands rejected for lacking support for the phrase "obtaining a DNA sequence of a genome" allegedly because the specification fails to describe obtaining less than the entire genome of an organism. The Office appears to rely on the sentence recited at page 7, line 5, of the application, which exemplifies obtaining the nucleotide sequence of the entire genome, asserting that this description precludes support for obtaining less than the entire genomic sequence.

The test for adequacy of written description is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed. *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (*citing Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Moreover, "[t]o comply with written description, it is not necessary that the application describe the claimed invention in *ipsis verbis*." *Application of Edwards*, 568 F.2d 1349, 1351-52 (C.C.P.A. 1978). The Federal Circuit has recently affirmed its long line of precedent in *Capon v. Eshhar*, Case Nos. 3-1480-1481, slip op. at 15 (Fed. Cir., August 12, 2005) where the Court emphasized that the written description requirement must be applied in the context of the particular invention and the state of the knowledge, declining to apply a *per se* rule requiring exact description of the invention as an inappropriate generalization.

Applicant maintains that the specification provides sufficient written description to satisfy the requirements of section 112, first paragraph. Federal Circuit precedent does not require *ipsis verbis* support and the Court has reaffirmed that all Applicants are not required to describe all inventions in the same way. Rather, as each field evolves so does the amount of description evolve that required to satisfy § 112, first paragraph. *Capon v. Eshhar*, Case Nos. 3-1480-1481, slip op. at 15 (Fed. Cir., August 12, 2005). Applicant respectfully submits that the Office's characterization that the application does not contemplate anything other than obtaining an entire genome fails to consider that the teachings in the specification are exemplary embodiments and not an *ipsis verbis* recitation of the only embodiment of how the invention works as claimed.

For example, the application teaches:

> **A process** 10 for producing metabolic genotypes from an organism is shown in Figure 1. Beginning at a star state 12, the process 10 then moves to a state 14 to obtain the genomic DNA sequence of an organism. The nucleotide sequence of the genomic DNA can be rapidly determined for an organism with a genome size on the order of a few million base pairs. **One method for obtaining the nucleotide sequences in a genome** is though commercial gene databases. Many gene sequences are available on-line though a number of sites (see, for example ww.tigr.org) and can easily be downloaded from the Internet.

Page 6, last paragraph (emphasis added).

Apparent from the above passage is that Applicant exemplifies one process for producing a metabolic genotype. For example, the process exemplified in Figure 1 is described as showing a process or one method for producing a metabolic genotype rather than the only process that can be employed. The sentence relied on for support by the Office exemplifies obtaining the sequence of an entire genome of an organism as another process that can be used for producing the claimed genome specific stoichiometric matrix (page 7, line 5). However, the sentence relied on by the Office does not require the entire genome be obtained for all embodiments of the claimed method.

Other teachings in the specification further clarify that obtaining the less than the entire genome of an organism was contemplated by the inventor at the time of filing. For example, the

application describes that a metabolic genotype can be constructed from less than all sequences in an organisms when it states:

> This invention relates to systems and methods for utilizing genome annotation data to construct a stoichiometric matrix representing most of all of the metabolic reactions that occur within an organism.

Page 6, lines 1-3 (emphasis added).

Apparent from the above description is that Applicant contemplated and expressly described that less than the entire genomic sequence of an organism can be employed in the methods of the invention. In this exemplary embodiment, Applicant characterized the amount of genomic sequence to obtain and employ in the methods of the invention as "most" rather than all or the entire genome of an organism. If Applicant had contemplated that only the entire genomic sequence could be utilized in the claimed invention he would not have included an express description to less than all of the genomic sequence.

Similarly, other descriptions within the application also expressly state that the claimed methods can be practiced through obtaining less than the entire genomic sequence. For example, the application describes:

> Thus, the functions of nearly the entire gene complement or genotype of an organism can be determined so long as homologous genes have already been discovered.

Page 7, lines 24-26 (emphasis added).

In this description, Applicant again chose words that clearly describe that less than the entire genome can be utilized in the method. In particular, use of the word "nearly" clearly shows that Applicant contemplated the use of a genomic sequences consisting of less than all.

Additionally, the application further exemplifies obtaining less than the entire genome sequence of an organism when it describes:

> Thus, the metabolic genotype of an organism includes most or all of the genes involved in the organism s metabolism.

Page 7, line 30 (emphasis added).

When taken in context of teachings such as the various passages cited above, the application clearly shows that Applicant was in possession of a method of producing a genome specific stoichiometric matrix that included embodiments where less than the entire genomic sequence of an organism was obtained. Use of words and phrases such as "a process," "one method," "most" or "nearly" provide express description that utilization of less than an entire genomic sequence was contemplated Applicant and described in the application. In contrast to the Office's assertion, these descriptions satisfy the written description requirement and withdrawal of this ground of rejection is respectfully requested.

Claim 53 also stands rejected for lack of written description allegedly because it does not require performing flux balance analysis to produce an *in silico* strain of the microbial organism. The Office again appears to adhere strictly to the embodiment exemplified in Figure 2, asserting that the specification does not describe the method in the absence of flux balance.

Applicant respectfully draws the Office's attention to the remarks made in their previous Response where it was explained that claim 53 is directed to a method of producing an *in silico* representation (see, for example, Applicant's Response beginning at page 7, para. 3). This method produces the claimed *in silico* representation by combining a genome specific stoichiometric matrix with physiological criteria such as metabolic demands and uptake rates and is described throughout the application including, for example, in the paragraph bridging pages 10-11. It is the *in silico* representation that contains the necessary information for computing possible phenotypes of an *in silico* model described in the application. However, until particular conditions are applied to the *in silico* representation, the representation does not predict any specific phenotype. Applying a particular set of conditions and computationally solving the representation for solutions to these conditions, implements or runs the *in silico* representation to model and provide the associated phenotypic behavior. Flux balance analysis is one method that can be applied to the *in silico* representation to compute solutions given a particular set of conditions to arrive at a specific *in silico* phenotype associated with the given set of conditions.

As previously pointed out, the application expressly describes both the generation of an *in silico* representation and the running of such an *in silico* model by computing phenotypic solutions using, for example, linear equations and/or flux balance analysis. For example, the

application describes that the genome specific stoichiometrix matrix is an underlying representation of an organism when it states:

> Thus, the process 50 moves to a state 58 in order to formulate all of the cellular reactions together in a genome specific stoichiometric matrix. The resulting genome specific stoichiometric matrix is a fundamental representation of a genomically and biochemically defined genotype.

Application at page 9, lines 14-17 (emphasis added). Further described is the determination and inclusion into the representation of metabolic demands and uptake rates (see, for example, page 9, lines 18-19, and page 9, lines 28-29). The applications also expressly describes application of, for example, linear equations and/or flux balance analysis to the fundamental representation for determination of a phenotype when it states:

> The particular utilization of the metabolic genotype can be defied as the metabolic phenotype that is expressed under those particular conditions. Objectives for metabolic function can be chosen to explore the 'best' use of the metabolic network within a given metabolic genotype.

Application at page 11, first paragraph.

In addition to these descriptions, Applicant respectfully points out that interpreting Applicant's description to require continuous production of the *in silico* representation or model and running of the representation to predict a particular phenotype given a set of conditions is inconsistent with the descriptions in the application as set forth above and in Applicant's previous response. Such an interpretation fails to account for the state of knowledge in the art and effectively applies a *per se* rule requiring applicant to claim nothing more and nothing less than the specific embodiment selected by the Office and exemplified in the Figures. The Federal Circuit has admonished the lower courts that the standard for satisfying the written description requirement should account for the state of knowledge in the art and that a *per se* rule is an inappropriate standard for satisfaction of the written description requirement. *Capon v. Eshhar*, Case Nos. 3-1480-1481, slip op. at 15 (Fed. Cir. August 12, 2005).

Computational processes require some underlying data or relationship in which to base a specific computational process. With respect to the claimed invention, the underlying structure is the *in silico* representation consisting of a stoichiometric matrix and can include metabolic

demands and uptake rates. In comparison, the computational process can employ a flux balance analysis to compute a specific metabolic phenotype. Applicant describes both the underlying data representation and associated mathematical characteristics producing the claimed *in silico* representation and also describes running the model to generate a specific phenotype associated with a given set of conditions. Such description is sufficient to show that Applicant was in possession of both the claimed method of producing the underlying representation and the claimed method of determining a genome specific metabolic phenotype. Requiring Applicant to restrict the invention to a specific embodiment exemplified in a figure is unduly limiting and is inappropriate, especially in light of the descriptions of the claimed *in silico* representation in the application and given the general knowledge in the art. Accordingly, Applicant respectfully requests that this ground of rejection be withdrawn.

Claims 57-61 stand rejected for lacking written description allegedly because providing only metabolic genes in an iterative process lacks support in the specification. The Office again maintains that the specification only contemplates selection of the subset of metabolic genes that are identified from ORF's of the genome, strictly adhering to the embodiment exemplified in Figure 1.

The written description requirement is satisfied if the application provides sufficient description to show that Applicant was in possession of the invention at the time of filing. *Vas-Cath Inc.* 935 F.2d at 1563-64; *Application of Edwards*, 568 F.2d at1351-52; *Capon*, Case Nos. 3-1480-1481, slip op. at 15. The Office's citation of *Lockwood v. American Airlines* fails to refute Applicant's proffered support because there is no factual showing or rational why the cited descriptions fail to provide sufficient support for the claimed invention. Rather, the conclusory statements that the cited descriptions do not support the claimed invention because they are fragmented is flawed by the fact that there is no reason as to why any one of them fail to support the objected term. For example, Applicant stated, *inter ala*, in the previous response:

> Moreover, the application describes supplementing steps of claim 57 when it teaches that additional reactions may be recognized upon review and included in the metabolic reaction list compiled by the claimed method.
>
> * * * * * * *

> [T]hat an *in silico* strain of *E. coli* was constructed that was "largely generated from annotated sequence data and from biochemical information" using "genetic sequence and open reading frame identifications and assignments [that are] readily available from a number of on-line locations (ex: www.tigr.org)."

Response at pages 9-10 (emphasis added).

Both of these descriptions show that the application describes step-wise processes. Other than offering a conclusory statements, the Office has failed to explain why either of these passages, or the other support cited by Applicant or described in the application, does not show Applicant's possession of the claimed invention. For example, setting forth that additional reactions may be recognized and added to the claimed method describes that the method can be performed in steps because there is no other mode available Similarly, querying and obtaining sequences from a public database inherently requires a step-wise process because each query sequence or criteria will be different.

Applicant additionally draws the Offices attention to the description in the application that describes that selectin of a subset of genes involves searching through the list of obtained genes. A search through a list involves a step-wise process. For example, the application describes:

> All of the genes involved in metabolic reactions and functions in a cell comprise only a subset of the genotype. This subset of genes is referred to as the metabolic genotype of a particular organism.
>
> * * * * * * *
>
> To begin the selection of this subset of genes, one can simply search though the list of functional gene assignments from state 18 to find genes involved in cellular metabolism.

Application at page 7, lines 27-29 and page 8, lines 4-5 (emphasis added).

The above descriptions from the application show that the application supports that the claimed method can be performed in an iterative fashion by either searching through a genome and selecting the open reading frames that encode metabolic genes or by obtaining metabolic genes directly from a database. Such a database is exemplified by the descriptions and references to on-line databases such as www.tigr.org. In light of these descriptions, Applicant

maintains that the application provides adequate written description for providing metabolic genes in an iterative process as is claimed. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 49 stands rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement. The Office alleges that, to the extent that claim 49 assigns function to every open reading frame in a microbial genome, the application lacks guidance as to how to proceed if an open reading frame has little homology to genes encoding proteins of known function. The Office further alleges, *inter ali*, that the declaration submitted by Dr. Subramaniam relies on criteria not included in the claims and is subjective, expressly denying any weight to the proffered evidence.

With regard to assignment of function to all open reading frames, Applicant does not claim assigning function to every open reading frame in a genome. The claim language clearly does not require determining the function of all open reading frames because it does not contain the terms "all" or "every," for example. Enablement "does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup International Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). Moreover, and as set forth previously, the application expressly teaches that less than all metabolic genes can be used in the methods of the invention.

Regarding the declaration, Dr. Subramaniam is an expert in the fields of bioinformantics and bioengineering. The evidence supporting Dr. Subramaniam's statements is supplied by, *inter ali*, the cited publication evidence and his curriculum vitae submitted as Exhibit I to the declaration. Criteria such as E-values relied on, in part, by the Office to refute the declaration such values are not elements of the claims appears to misinterpret the fact that these characteristics were pointed out by Dr. Subramaniam for the purpose of exemplifying that such homology methods were well known to those skilled in the art. Regarding the express denial of any weight accorded to Dr. Subramaniam's declaration, Applicant respectfully requests that the Office cite the appropriate legal authority for such action. According to the Court of Custom and Patent Appeals and Federal Circuit precedent opinion testimony is entitled to consideration and weight so long as the opinion is not directed to the ultimate legal conclusion at issue. Even where an opinion is on the ultimate legal, the underlying basis for deciding such a legal

conclusion is entitled to some weight. *In re Chilowsky*, 306 F.2d 908 (C.C.P.A. 1962). Moreover, in assessing the probative value of an expert opinion, the Office must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986).

Applicant has submitted a declaration by an expert attesting that statements made in the application regarding well known methods were accurate. The declaration does not draw an ultimate legal conclusion that the application is enabled. Rather, the declaration cites to publication evidence supporting the conclusion that, at the time the application was filed, it was well established in the art that sequence homology could be used to establish function. The declaration further provides facts, citing to databases and algorithms such as the BLAST and FAST family of programs, that were well known to be used for determining sequence homology. For example, Dr. Subramaniam attests:

> [I]t was well established at the time the priority application was filed on February 2, 1999, that those open reading frames that have appropriate sequence homology with genes from other microbes whose function was previously assigned could be characterized to possess the same function. . . . [D]atabases such as COG (Complete Groups of Orthologous Genes, National Institutes of Health Website that uses bi-directional BLAST; http://www.ncbi.nlm.nig.gov/COG/; *Science* 1997 Oct 24; 278(5338):631-37) have criteria that are routinely deployed for function identification through homology.

Declaration at para. 4 (emphasis added).

Accordingly, Applicant did not submit an opinion declaration drawing ultimate legal conclusions. The declarant cited to publication and factual evidence as a basis of his statements. The declarant lacks an interest in the outcome of this issue and the strength of the opposing evidence is minimal, consisting solely argument by the Office. In light of this showing, Applicant has satisfied his burden that one could assign function to an open reading frame based on sequence homology. Applicant respectfully requests that the declaration be accorded its proper weight as an opinion declaration by an expert in the field anchored by a factual basis and that this ground of rejection be withdrawn.

Regarding guidance on how one assigns function to an open reading frame, Applicant respectfully refers the Office to the above remarks, Dr. Subramaniam's declaration and the teachings in the application as well as references thereto of record. Such methods were well known in the art and provide sufficient teachings and guidance to allow one skilled in the art to practice the methods as described and claimed. Accordingly, Applicant respectfully requests that this ground of rejection be withdrawn.

Claims 54-55 and 64-64 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because they either lack an antecedent basis or are unclear.

Claims 55 and 63 have been cancelled. Accordingly, these grounds of rejection are moot.

With respect to claims 54 and 65, Applicant maintains that these claims further limit their base claims and draw the Office's attention to the remarks of record. Applicant is unaware of any admission that such claims do not properly further limit base claims 53 and 61, respectively. As described previously and above:

> The resulting genome specific stoichiometric matrix is a <u>fundamental representation</u> of a genomically and biochemically defined genotype.

Application at page 9, lines 14-17 (emphasis added).

Accordingly, the *in silico* representation corresponds to the underlying metabolic genotype of, for example, stoichiometry, reactants and products that is combined with, for example, metabolic demands and rate information. The *in silico* representation is solved for a particular phenotype given a set of conditions using, for example, linear equations or flux balance analysis. Therefore, these claims do further limit the base claim and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 49-51, 53-59 and 61-65 stand rejected under 35 U.S.C. § 102(b) as anticipated by Schilling et al. The Office alleges that Applicant is entitled to the filing date corresponding to the continuation application allegedly because the newly introduced claims constitute new matter. Schilling et al. is further alleged to anticipate the claimed invention because it was published prior to the filing date of the continuation application.

While not conceding that Schilling et al. describes each and every element of the invention claimed in claims 49-65, Applicant has set forth previously that the claims as filed in the continuation application are adequately supported in the application as of the priority date. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 52 and 60 stand rejected under 35 U.S.C. § 103(a) as obvious over Schilling et al. as applied to claims 49-51, 53-59 and 61-65 above and further because the use of BLAST would have been obvious to those skilled in the art allegedly because it is a well known search tool.

While not conceding that Schilling et al. teaches or suggests the claimed invention, Applicant has set forth previously that the claims as filed in the continuation application are adequately supported in the application. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Claims 49-65 stand rejected under 35 U.S.C. § 103(a) as being obvious over Blattner et al., Pennisi, Edwards et al. (1997) and Pramanik et al. for the reasons of record. In particular, The Office alleges that it would have been obvious to produce a stoichiometric matrix and an *in silico* model of *E. coli* and *H. influenzae* according to Pramanik et al. using the sequences and assignments in Blattner et al. and Pennisi et al. because such models would have been of interest and within the skill of the art to produce as seen by Edwards et al. The Office further contends that Applicant's remarks are unpersuasive apparently because the cited support over Pramanik et al. does not exist. The Office alleges that there is no page 3 in Pramanik et al., that the specification does not discuss this reference and that the Office is unclear why this reference teaches away from the claimed invention.

Applicant respectfully points out that the support cited to was directed to the description of Pramanik et al. in the application. Applicant apologizes for citing to page 3 rather than page 4 of the application. Further, Applicant's reasons why Pramanik et al. teach away from the claimed invention also was clearly stated in the previous response. The reference to the application and reasons for teaching away were clearly stated in the following passage:

> [A]s described in the subject application at, for example, page 3, first paragraph, Pramanik et al. teach away from using models that are not produced from existing biochemical information. . . . The cited combination of references fail to teach, suggest or provide a motivation to construct a stoichiometric matrix as claimed because Pramanik et al. teach away from generating a metabolic model absent actual knowledge of biochemical information. Therefore, Pramanik et al. is inapplicable in combination with a model purporting to use only genomic information such as Edwards et al. is alleged to describe. Accordingly, the cited art does not render the invention obvious and withdrawal of this ground of rejection is respectfully requested.

Response filed January 21, 2005, at page 17 (emphasis added).

> Pramanik et al. is distinguished in the application where it describes:
>
> In one example, Pramanik et al. described a stoichiometric model of E. coli metabolism using flux-balance modeling techniques (*Stoichiometric Model of Escherichia coli Metabolism: Incorporation of Growth-Rate Dependent Biomass Composition and Mechanistic Energy Requirements*, *Biotechnology and Bioengineering*, Vol. 56, No. 4, November 20, I 997). However, the analytical methods described by Pramanik, et al. can only be used for situations in which biochemical knowledge exists for the reactions occurring within an organism. Pramanik et al. produced a metabolic model of metabolism for *E. coli* based on biochemical information rather than genomic data since the metabolic genes and related reactions for *E. coli* had already been well studied and characterized. Thus, this method is inapplicable to determining a metabolic model for organisms for which little or no biochemical information on metabolic enzymes and genes is known. It can be envisioned that in the future the only information may have regarding an emerging pathogen is its genomic sequence.

Application, page 4, first paragraph (emphasis added).

Accordingly, the cited combination of references fail to teach, suggest or provide a motivation to construct a stoichiometric matrix as claimed because Pramanik et al. teach away from generating a metabolic model absent actual knowledge of biochemical information. Therefore, Pramanik et al. is inapplicable in combination with a model purporting to use only genomic information such as Edwards et al. is purported to describe. In light of the above remarks, the cited art does not render the invention obvious and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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